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Copper-Catalyzed Ring Opening of [1.1.1]Propellane with Alkynes: Synthesis of Exocyclic Allenic Cyclobutanes

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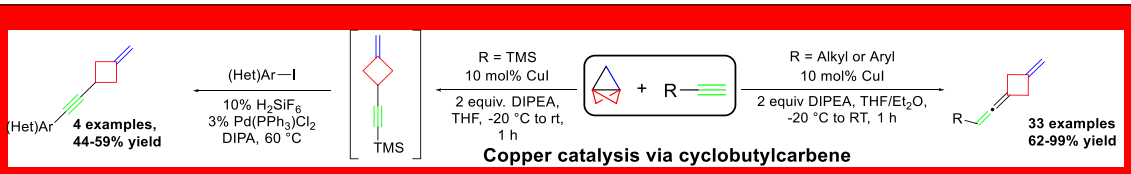
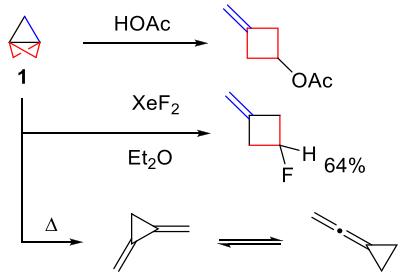
Supporting Information



Despite the long history and interesting properties of propellanes, these compounds still have tremendous potential to be exploited in synthetic organic chemistry. Herein we disclose an experimentally simple procedure to achieve cyclobutane-containing allenes and alkynes through a copper-catalyzed ring opening of [1.1.1]propellane and subsequent reaction with ethynes.

Propellanes are fascinating molecules.[1] The unique structure and behavior of these molecules have captivated the imagination of chemists from the time they were predicted to exist to the present day.[2] Their most interesting properties include high ring strain and the "inverted" charge-shift type central C−C bond.[3] This property can be used to open up [1.1.1]propellane (**1**) in various interesting ways. Owing to the practical preparation of **1** developed by Szeimies,[4] most of the available synthetic methods are aiming for the valuable [1.1.1]bicyclopentane scaffold in one or more steps.[5] On the other hand the ring opening to cyclobutanes are not widely explored (Scheme 1). The first synthesis of **1** was immediately

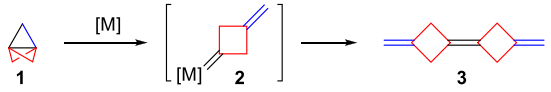
Scheme 1. Ring-Opening Reactions of [1.1.1]Propellane



followed by showcasing the double ring opening by acetic acid.[6] This ring opening can also be achieved by XeF_2 in ether, resulting in fluorinated cyclobutane.[7] Szeimies and Walsh ran a series of interesting experimental and theoretical studies of thermal ring opening of propellane in the gas phase. Their calculations show the intermediate is reminiscent of a cyclobutylcarbene and bicyclo[1.1.0]butane. This intermediate then rearranges to various cyclopropanes.[8]

In contrast to the reactions of bicyclo[*n*.1.0]alkanes with nickel,[9] the chemical properties of **1** in the presence of transition metals are scarcely examined in the literature.[10] One of the most comprehensive early studies on the reactions of [1.1.1]propellane briefly mentions these kinds of reactions.[11] Wiberg and Waddel found analytical evidence that **1** in the presence of transition metals is prone to undergo dimerization and trimerization (Scheme 2). This might happen through a

Scheme 2. Transition-Metal-Catalyzed Ring Opening of 1



carbenoid intermediate (**2**). Despite the potentially interesting cyclobutane products, no synthetic study was done on this catalytic type of ring opening of [1.1.1]propellane. This might be due to the fact that cyclobutylidenecarbenes are known to undergo various kinds of rearrangements by C−C or C−H insertion of the carbene in an intramolecular manner.[12]

We were interested in exploring the chemical behavior of [1.1.1]propellane over various transition metals and exploiting their chemical behavior in synthetic methods. Our starting experiments have confirmed the earlier observed dimerization phenomena over Pd and Pt catalyst. In our hand, dimerization could also have been induced by iron(II) chloride[13] and copper iodide.

Our attempts to utilize this carbenoid to cyclopropanate double bonds are yet unsuccessful, but recent publications on the application of copper carbenoids in reactions of alkynes[14] raised the possibility of a synthetic procedure to gain valuable allenic cyclobutane product **6** through **5a** or **5b** (Scheme 3).

Crabbé-like allene synthesis has great limitations with cyclic products,[15] and only a few other catalytic methods are able to build up alkylidenecyclobutanes. Those often utilize complex

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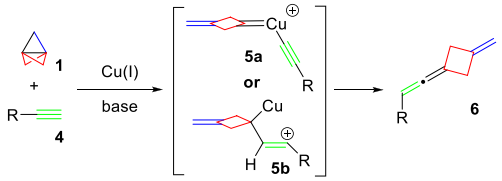
Scheme 3. Envisioned Reaction Mechanism



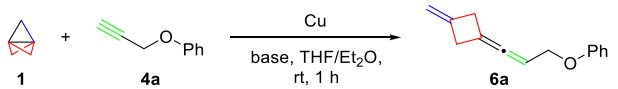
and expensive starting materials and catalysts.[16] On the other hand, the methylidenecyclobutane scaffold is present in biologically interesting natural products, as the pink hibiscus mealybug sex pheromone,[17] or it is used as key intermediate during total synthesis.[18]

According to the few literature precedents, ring strain enhances the formation of the alkyne product instead of an isomer exocyclic allene.[19] This effect is more notable with cyclopropanes and earlier described synthetic procedures to obtain exoallenic cyclobutanes, which suffered from the formation of isomeric mixtures.[20]

It is noteworthy that allenes are also important in pharmaceutical applications, such as in enprostil,[21] and as a synthetic building block.[22] Therefore, we aimed to develop a simple synthetic method to build up this cyclobutane-containing scaffold.

With this goal in mind, we identified optimal conditions for the reaction of phenylpropargyl ether (**4a**) and **1**, which resulted in the conditions in Table 1, entry 1. To offer deeper insight into this reaction, some alternative conditions are shown in Table 1.[23]

Table 1. Optimization of Reaction Conditions



entry	catalyst	base	**1** (equiv)	yield[a] (%)
1	**CuI (0.1 equiv)**	**DIPEA (2 equiv)**	**1.5**	**99**
2		DIPEA (2 equiv)	1.5	0
3	Cu(*acac*)$_2$ (0.1 equiv)	DIPEA (2 equiv)	1.5	20
4	Cu(OAc)$_2$ (0.1 equiv)	DIPEA (2 equiv)	1.5	57
5	CuCl (0.1 equiv)	DIPEA (2 equiv)	1.5	95
6	CuI (0.01 equiv)	DIPEA (2 equiv)	1.5	99
7	CuI (0.15 equiv)	DIPEA (2 equiv)	1.5	99
8	CuI (0.1 equiv)	DIPEA (2 equiv)	1.0	86
9	CuI (0.1 equiv)	TEA (2 equiv)	1.5	98
10	CuI (0.1 equiv)	DBU (2 equiv)	1.5	12
11	CuI (0.1 equiv)	Cs_2CO_3 (2 equiv)	1.5	0
12	CuI (0.1 equiv)	DIPEA (1 equiv)	1.5	89
13	CuI (0.1 equiv)	DIPEA (5 equiv)	1.5	99

[a]Determined by GC−MS. Starting from 0.5 mmol of **4a**

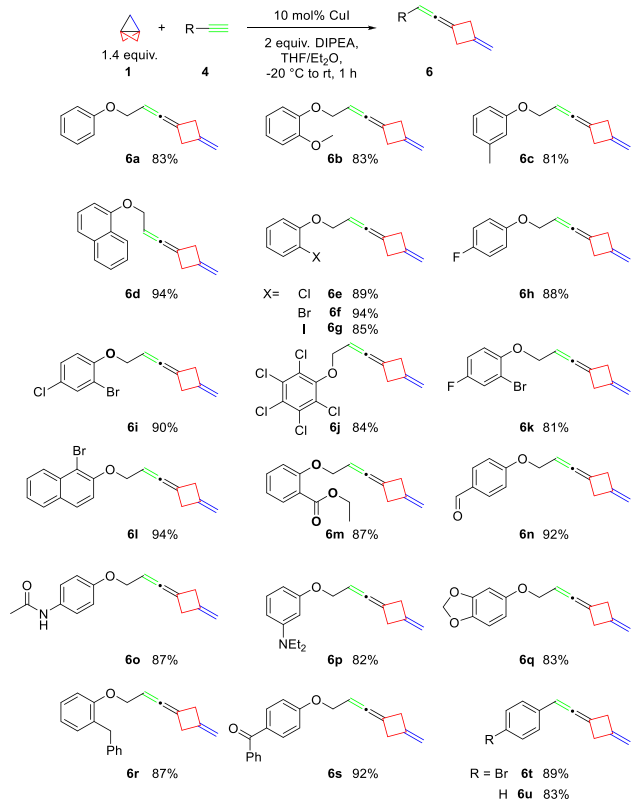
In contrast to our optimal conditions, it was confirmed that the addition of catalyst is crucial for the reaction (entry 2), but other explored copper catalysts did not lead to a complete conversion of the alkyne. The only observed exception was CuCl (entry 5), but due to the inseparable impurities it was proven to be impractical for use, in contrast to the air-stable CuI, which gave the allene as the only observable product. The amount of CuI did not play a crucial role (entries 6 and 7), as little as 1% led complete conversion. For the sake of experimental convenience, 10 mol % of CuI was used.

During the preparation of the scope, we had a reproducibility issue while changing batch of copper iodide. A minor inseparable impurity of about 5% appeared in the reaction mixture. The main important factor turned out to be the purity of copper source. CuI with a purity of 99.999% did not produce the unidentified side product. After experimenting with different copper iodide sources, we found that most of them do not support this side product formation.

Lowering the amount of propellane solution resulted in a slightly inferior result (entry 8). The base plays an important role in removing the proton from **4**. A 2 equiv amount of non-nucleophilic Hünig's-base was utilized to achieve the best result in yields and reproducibility, but good yields could be achieved by TEA as well (entry 9). Addition of DBU (entry 10) was inferior to weaker bases, as it resulted in side reactions in our hand. No conversion of **4a** was observed with inorganic base Cs_2CO_3. This reaction is very robust to the variation of solvent; thus, technical-grade THF was used. The transformation generally takes place in 30 min; however, for convenience, 1 h reaction time was set as the standard in the optimized conditions.

It was important to establish a scope in order to prove the general utility of this reaction (Scheme 4). Various propargyl ethers have been converted to the corresponding allene **6**. As expected, the electronic properties on the phenyl part did not play crucial role in the observed yields, as compounds with electron-donating and -withdrawing substituents worked with equal efficiency to provide the products. Starting materials

Scheme 4. Scope of the Reaction with Terminal Alkynes[a]



[a]Alkyne (1 mmol), [1.1.1]propellane (1.4 mmol), isolated yields.

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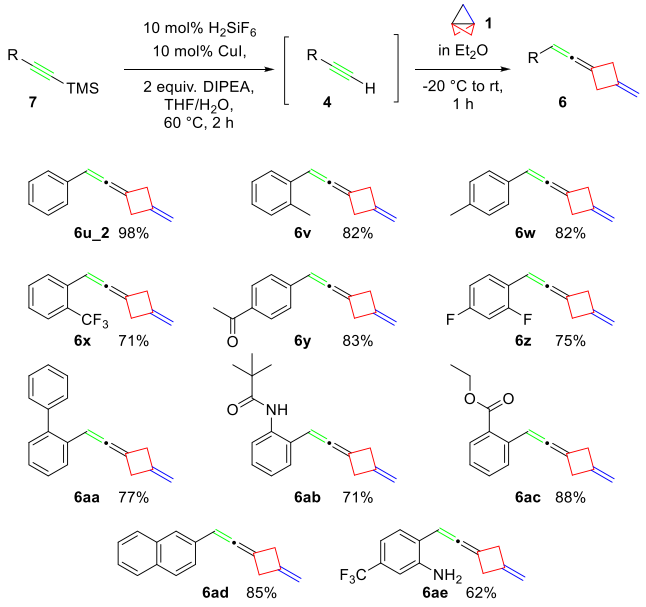
bearing aryl halides were converted to the corresponding cyclobutanes (**6e**–**l**), offering a wide range of products through cross-coupling or cyclization. The procedure was able to convert alkynes bearing functional groups such as ester (**6m**), aldehyde (**6n**), amide (**6o**), or amine (**6p**) into the exocyclic allenes in good to excellent yields.

Finally, 4-bromophenylacetylene and phenylacetylene (**4t**,**u**) was also effectively converted to the corresponding exoallenic cyclobutane. The last reaction of this table was extended to 10 mmol scale, providing **6u** in the same yield (83%, 1.38 g) as 1 mmol.

Other aromatic alkynes are not readily available, so we turned our attention to silylacetylenes. These are easy to make via Sonogashira coupling from aryl halides and TMS-acetylene. Our recent findings on a simple catalytic desilylation strategy, with the cheap and nontoxic water solution of hexafuorosilicic acid,[24] encouraged us to develop a one-pot procedure directly from silylalkynes. In the conditions of the cyclobutylation, the desilylation by catalytic H_2SiF_6 occurred smoothly and gave free terminal alkyne. This acetylene could be used in situ for the reaction with **1**, avoiding an extra step in the preparation of such substances. In this manner, a range of cyclobutanes were synthesized. (Scheme 5). In general, high yields have been

Scheme 5. Substrate Scope from Silylacetylenes[a]



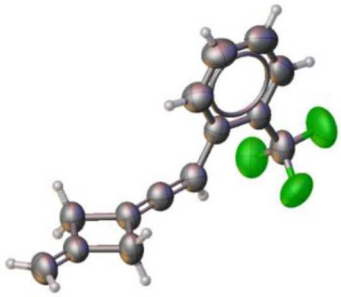
[a]Silylalkyne (1 mmol), [1.1.1]propellane (1.5 mmol), isolated yields.

observed for these products derived from 1-aryl-2-silylalkynes. It was possible to synthesize arylallenes in this manner, including ones bearing keto (**6y**), amide (**6ab**), or ester (**6ac**) functional groups. Even a trifluoromethylated aniline derivative, **6ae** was transformed to the corresponding cyclobutane.

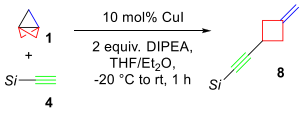
To gain more knowledge on this novel structural motif, we attempted to acquire information on its structure. We were able to produce a suitable single crystal of **6x** for X-ray spectroscopy (Scheme 6). As expected, the new scaffold is a linear motif with a 6.025 Å distance from the first allene carbon to the methylidene.

In the case of 1*H*-2-silylacetylenes, exclusive alkynylcyclobutane (**8**) formation was observed. It is possible that the sterical hindering and electron donating the effect of the silyl

Scheme 6. X-ray Structure of Product 6x

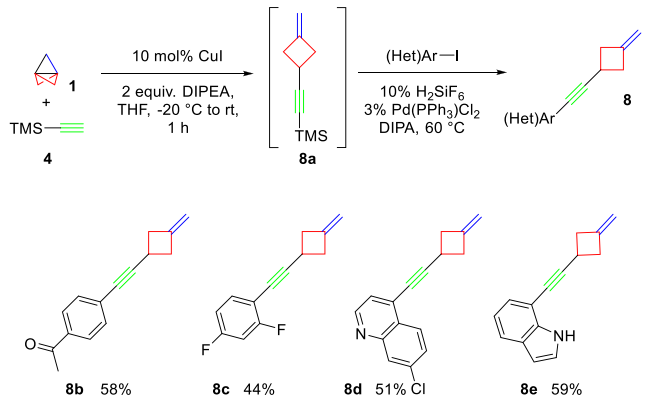


groups making the cyclobutylcopper intermediate more nucleophilic; thus, it is easier to directly protonate it.



Both TIPS and TMS acetylene form in high efficiency, over 85 and 95% GC conversion, respectively, but these product molecules remain a challenge in gaining a pure form due to their apolar character or volatility. In contrast, it is convenient to exploit this phenomenon in the preparation of different alkynycyclobutanes. The product 1-methylidene-3-alkynylcyclobutanes are not easy synthetic targets, as only a handful of compounds were found in the literature, made by cyclization,[25] or Wittig reaction in a very low yield while preparing some antibacterial agents.[26] Again, hexafluorosilicic acid came handy in this step for the one-pot Sonogashira coupling. The TMS-alkynyl cyclobutane **8a** was converted into various aromatic and hetroaromatic products **8b**–**8e** (Scheme 7).

Scheme 7. Synthesis of Alkynylcyclobutanes through TMS Acetylene[a]



[a]Alkyne (1 mmol), [1.1.1]propellane (1.4 mmol), isolated yields.

Regarding the mechanism, radical ring opening of **1** seems unlikely, as such a rearrangement has a very high activation energy barrier.[27] To confirm the absence of activity of radicals in this reaction, 0.1 and 1 equiv of TEMPO was added to the reaction mixture (Scheme 8). This had no effect on the outcome of the reaction. Somewhat surprisingly, we did not even observe the product of the reaction of **1** and TEMPO, which emphasizes the fast reaction rate of ring opening by copper. Deuterated acetylene was allowed to react this time in

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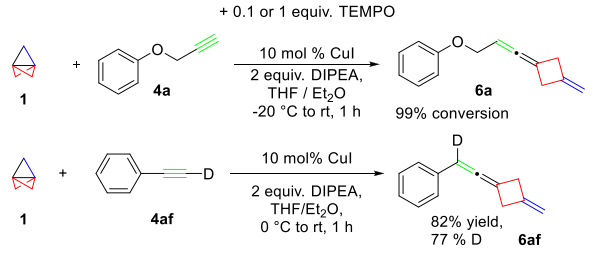
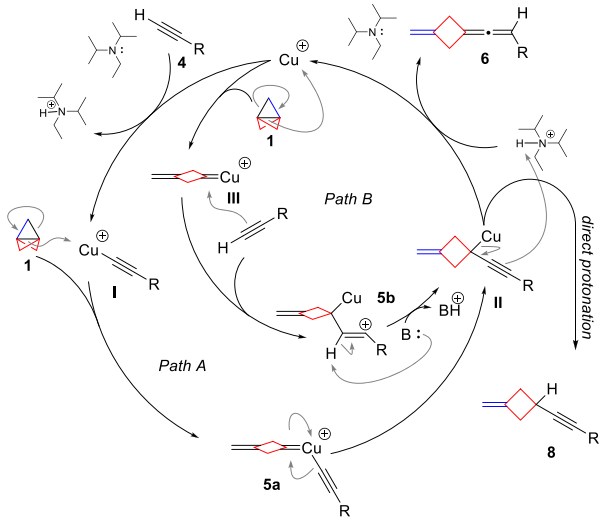
Scheme 8. Mechanistic Investigation



anhydrous THF, to give product in a level of deuteration of more than 75% (**6af**).

Recent experimental and computational results from the field of allene synthesis from hydrazones can provide some suggestions for the mechanistic cycles.[14b,d,f] It is possible (Scheme 9, path A) that from **4** in the slightly basic condition

Scheme 9. Depicted Working Hypotheses



with copper a Cu acetylide (**I**) forms. This copper(I) species is able to coordinate to **1** through its charge shift type central bond, causing the ring opening that gives **5a**. Then carbene insertion occurs, resulting in alkynyl cyclobutane (**II**).

The other envisioned route (path B) is more similar to the one calculated by Bai to be lower in energy in the case of carbenes generated from hydrazones. In the first step, the cyclobutylcarbene (**III**) is formed. This is then attacked by the terminal acetylene to give a vinylcation intermediate (**5b**), which is deprotonated by the base, resulting in **II**. The strong electron-donating property of silyl groups might facilitate the direct protonation of this intermediate, while in other observed cases rearrangement happens to the allene **6**.

Starting from copper phenylacetylide, only traces of the allene product were observed, with or without added base. When nonanhydrous conditions were used, starting from isotope-labeled phenylacetylene, the extent of deuteration in **6af** only slightly dropped to 55%, suggesting the proximity of the conjugated base. This both might support path B.

In conclusion, an obscure intermediate, namely a cyclobutylidenecarbene, was utilized in a remarkably simple synthetic procedure to produce valuable cyclobutanes. This new concept allowed us to synthesize cyclobutanes with allenes and alkynes. Our approach deliberates the opportunity to explore similar ring opening pathways to use the resulting carbenes generated from strained propellanes in various organic reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03999.

Experimental details; spectra of products (PDF)

Accession Codes

CCDC 1947306 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to the memory of Professor Dr. György Hajós.

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